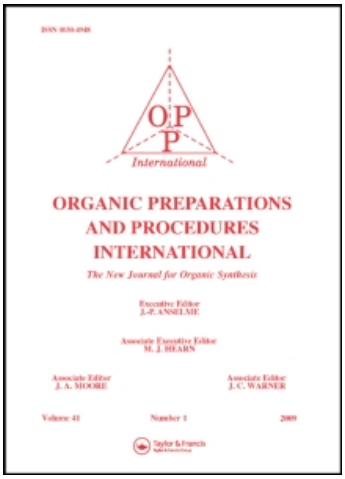

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EXPEDITIOUS ROUTES TO SYMMETRICALLY AND ASYMMETRICALLY SUBSTITUTED PYRIDINES FROM CHELIDAMIC ACID

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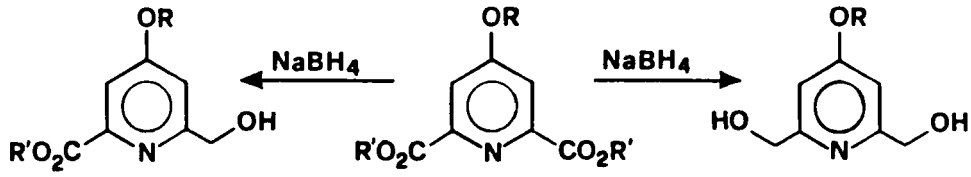
Growing interest in ligands for the synthesis of models of metalloenzymes or metalloreceptors has prompted the quest for straightforward methodologies to symmetrically or asymmetrically functionalized heterocycles; among these, pyridine[1] plays an important role. For instance, Cram[2] and Bradshaw[3] and their groups synthesized pyridino crown ethers; Lehn,[4] Burrows[5] and our group[6] have synthesized pyridinocyclophanes. Furthermore, 4-alkoxypyridines have proved to be key building blocks in the synthesis of fairly effective bleomycine models.[7] During our investigation of hydrolytic metallosurfactants[8] and metalloreceptors,[5] we became interested on the synthesis of 4-oxysubstituted pyridines bearing the same or different functional groups at the 2- and 6-positions. The diester of commercially available chelidamic acid (1,4-dihydro-4-oxo-2,6-pyridinedicarboxylic acid) appeared to be an ideal starting material. Reports on the literature on its reduction are contradictory. Bradshaw and Izatt[9] described the reduction of the O-protected ester of chelidamic acid 1a (THP = tetrahydropyranyl) to diol 3a with $NaBH_4$ in ethanol, while Ohno[7] reported the conversion of 1b to alcohol 2a using the same reducing agent in methanol. We now report a simple and clean procedure for the synthesis of the mono- or dialcohol, as shown below.



2 1 3

a) R = R' = Me
b) R = THP, R' = Et
c) R = H, R'. = Et

a) R = THP, R' = Me
b) R = R' = Me
c) R = THP, R' = Et
d) R = H, R' = Et

a) R = THP
b) R = H

The OH-protected diester (1c) is converted to 2b with $NaBH_4$ while it is reduced to 3a in the presence of the stoichiometric amounts of $CaCl_2$;[10] on the other hand the OH-free diester 1d is reduced to 2c cleanly at 25° with $NaBH_4/CaCl_2$. The reduction products of the non-protected ester are sparingly soluble in organic solvents thus rendering their isolation as pure materials quite troublesome. Since the THP-protected derivative may be selectively converted to 2 or 3 with or

without the addition of $CaCl_2$ and the products worked up without major problems, we strongly recommend the use of the THP-protected starting material. Once the THP-protected alcohol (2 or 3) is obtained, deprotection is easily performed in acidic methanol in 30 min at 25°. By the use of standard procedures, these derivatives may be further functionalized (aldehyde,[11] chloride[12]) and, therefore, constitute excellent building blocks for a variety of pyridine functionalized macrocycles.

EXPERIMENTAL SECTION

Chelidamic acid and $NaBH_4$ were purchased from Aldrich and used as received. Freshly distilled dry EtOH was used throughout. The diethyl ester 1d was obtained by refluxing the acid in EtOH in the presence of H_2SO_4, as reported.[13] The protection of the diester with dihydropyran was performed according to the literature.[13] NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz and chemical shifts are reported in δ units using TMS as internal standard. Melting points are uncorrected. Elemental analyses were performed by the Laboratorio di Microanalisi of our Department.

General Procedure.- To a stirred solution of ester (4.2 mmol) in 25 mL of dry EtOH, was added in portions, $NaBH_4$ (2.1 mmol to give 2; 4.2 mmol to give 3) at 25°. Some hydrogen evolution occurred with concomitant increase of the temperature. If necessary, finely powered $CaCl_2$ (2.1 or 4.2 mmol, see above) was added *cautiously* in small portions and the evolution of H_2 was allowed to cease before each further addition. The reaction mixture was then stirred at 25° (2 hrs for the reduction with $NaBH_4/CaCl_2$ and 12 hrs for the reduction with $NaBH_4$). When the reaction was completed H_2O (100 mL) was added; in the case of the non-protected derivative, the pH was adjusted to 6 with 1N HCl. Two different procedures were followed for the OH-protected or non-protected material.

Owing to the high hydrophilicity of the *OH-free starting material*, the aqueous solution was continuously extracted with $CHCl_3$ for 6 days to give 2c in 90% yield. Compound 3b could not be recovered from the aqueous phase even with longer extraction times (see below for compound characterization). In the case of the *THP-protected starting material*, the ethanol was evaporated in vacuo, brine was added (50 mL) and the mixture extracted with $CHCl_3$ (4 x 200 mL). Evaporation of the dried (Na_2SO_4) organic solvent afforded 2b as an oil after chromatography over silica ($CHCl_3$/EtOH, 9:1), or 3a as a white solid, mp. 116-117° (from CH_2Cl_2/pentane) in 81 and 92% yields respectively. ^1H NMR of 2b ($CDCl_3$): δ 1.35 (t, 3H, CH_3); 1.43-1.95 (m, 6H, $3CH_2$THP); 3.4 (br s, 1H, OH); 3.6-3.85 (m, 2H, OCH_2THP); 4.45 (q, 2H, CH_2CH_3); 4.75 (s, 2H, OCH_2Py); 5.60 (m, 1H, CHTHP); 7.10 and 7.60 (2d, 2H, Py H3 and H5). ^1H NMR of 3a ($CDCl_3$): δ 1.43-2.01 (m, 6H, $3CH_2$THP); 3.0 (br s, 2H, 2OH); 3.60-3.85 (m, 2H, OCH_2THP); 4.75 (s, 4H, $2OCH_2$); 5.55 (m, 1H, CHTHP); 6.80 (s, 2H, Py H3 and H5).

Deprotection was achieved by dissolving the alcohol in CH_3OH (100 mL) containing 0.5 mL of conc. HCl. After stirring for 0.5 hr, the solvent was stripped to leave the OH-free derivatives.

Characterization of 2c: mp. 150-151° (from $CHCl_3$/pentane); ^1H NMR (CD_3OD): δ 1.50 (t, 3H, CH_3); 4.65 (q, 2H, CH_2CH_3); 5.04 (s, 2H, OCH_2Py); 7.06 and 7.57 (2d, 2H, Py H3 and H5).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.96; H, 5.61; N, 7.09

Characterization of 3b: mp. 148-150° (from EtOH/Et_2O); ^1H NMR ($CDCl_3/CD_3OD$, 10:1): δ 4.80 (s, 4H, $2CH_2$), 7.10 (s, 2H, Py H3 and H5).

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.25; H, 5.80; N, 8.95

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REFERENCES

1. V. K. Majetic and G. R. Newkome, Top. Curr. Chem., 106, 79 (1982); G. R. Newkome, J. D. Sauer, J. M. Roper and D. C. Hager, Chem. Rev., 77, 513 (1977); S. M. Nelson, Pure Appl. Chem., 52, 2461 (1980).

2. M. Newcomb, J. M. Timko, D. M. Walba and D. J. Cram, J. Am. Chem. Soc., 99, 6392 (1977).

3. J. S. Bradshaw, G. E. Maas, J. D. Lamb, R. M. Izatt and J. J. Christensen, ibid., 102, 467 (1980); J. S. Bradshaw, N. O. Spencer, G. R. Hansen, R. M. Izatt and J. J. Christensen, J. Heterocycl. Chem., 20, 353 (1983).

4. J.-M. Lehn, Pure Appl. Chem., 52, 2441 (1980).

5. C. A. Salata, D. Van Engen and C. J. Burrows, Chem. Commun., 579 (1988).

6. R. Fornasier, F. Reniero, P. Scrimin and U. Tonellato, J. Incl. Phenom., 6, 175 (1988).

7. A. Kittaka, Y. Sugano, M. Otsuka and M. Ohno, Tetrahedron 44, 2821 (1988).

8. R. Fornasier, P. Scrimin, P. Tecilla and U. Tonellato, J. Am. Chem. Soc. 111, 224 (1989).

9. Y. Nakatsuji, J. S. Bradshaw, P. K. Tse, G. Arena, B. E. Wilson, N. K. Dalley and R. M. Izatt, Chem. Commun., 749 (1985).

10. $Ca(BH_4)_2$ is quite likely the reducing species formed *in situ*. See: M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 2, p. 57; Wiley, New York, 1969.

11. U. Luning, R. Baumstark, K. Peters and H. G. von Schnering, Ann., 129 (1990).

12. P. Scrimin, P. Tecilla, U. Tonellato and T. Vendrame, J. Org. Chem., 54, 5988 (1989).

13. J. S. Bradshaw, M. L. Colter, Y. Nakatsuji, N. O. Spencer, M. F. Brown, R. M. Izatt, G. Arena, P. K. Tse, B. E. Wilson, J. D. Lamb, N. K. Dalley, F. G. Morin and D. M. Grant, ibid., 50, 4865 (1985).

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